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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/085,906	02/27/2002	Vincent Ling	GNN-5343CP2	5219

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EXAMINER	
SWITZER, JULIET CAROLINE	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 01/05/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/085,906	LING ET AL.	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 June 2004 and 14 October 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,10-12,15 and 16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,10-12,15 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 June 2004* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This office action is written in response to applicant's correspondence filed 6/10/04 and 10/14/04. Claims 4, 5, 10, and 12 have been amended. Claims 7-9 and 13-14 have been cancelled. Claims 15-16 have been added. Claims 1-6, 10-12, and 15-16 pending and are under prosecution, and claims which recite particular PMR sequences have been examined only insofar as they recite the elected PMR sequence and associated primers (SEQ ID NO: 352-354).

2. All of the amendments and arguments have been considered but are not sufficient to place the claims in condition for allowance for the reasons discussed in this office action. All current grounds for rejection are set forth, and applicants remarks are addressed following the rejections.

3. **This action is FINAL.**

Sequence Rules Compliance

4. This application is in compliance with the sequence rules.

Drawings

5. The drawing filed on 6/10/04 is not acceptable because the lettering in the drawing is too small to read. The drawing appears to be a facsimile of a copy of a drawing, and though the proper sequence identifiers are added in the copy, in the new copy of the drawing the actual sequences are illegible. A corrected drawing is required, and this requirement cannot be held in abeyance.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-6, 10-12, 15, and 16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Nature of the Claims

Claims 1-6 and 15 are drawn to a method for determining the predisposition of a human subject to develop autoimmune disease via the detection of at least one polymorphic microsatellite repeat (PMR) in the human costimulatory receptor gene locus, wherein the PMR sequence is not an hR2 sequence. The nature of the claimed invention is such that the practice of the invention is dependent on the knowledge of a relationship between PMR alleles and particular diseases or all autoimmune diseases.

Claims 10-12 and 16 are drawn simply to determining the polymorphic variant or subtype of a PMR sequence within the CTLA4 gene of the human costimulatory receptor gene locus, wherein the PMR is not an hR2 sequence. Claim 11 is limited to the detection of the PMR SEQ ID NO: 354. The nature of this claimed invention is such that to use the claimed invention one must have some knowledge of how to apply the information gained from determining the polymorphic subtype in question.

Breadth of the Claims

Claims 1-3 and 5-6 are broadly drawn to the determination of a predisposition to any possible autoimmune disease, a disease classification which includes a wide variety of diseases of varying effects and etiologies. This is exemplified in claim 4 which recites a listing of some

possible autoimmune diseases, including insulin-dependent diabetes mellitus, lupus, leprosy, and rheumatoid arthritis. Newly added claim 15 is also drawn to the determination of a predisposition to any possible autoimmune disease, but comprises detecting only the PMR of SEQ ID NO: 354.

Further, claims 1, 4, and 5 are broadly drawn to include detecting any polymorphic microsatellite repeat (PMR) within the human costimulatory receptor gene locus, wherein the PMR sequence is not an hR2 sequence. With regard to the detected PMR, claims 2, 3, 6, and 15 are limited to the elected PMR sequence which is within the CTLA-4 gene (p. 12 of the spec).

Claims 10, 12, and 16 are broadly drawn to include detecting any PMR within the "CTLA4 gene," a region which is not clearly defined in the specification but is broadly interpreted to include the region of the genome that includes exons encoding the CTLA4 gene as well as intergenic regions that are upstream and downstream of this region.

The all of the rejected claims specifically exclude the use of an "hR2 sequence" within the claimed methods. As noted in the 112 2nd rejection herein, the scope of this exclusion is unclear. The prior art is silent with respect to any sequence in the CTLA4 gene or any other gene in the costimulatory receptor locus that is called the hR2 sequence. With regard to hR2, the specification teaches that IDDM, Grave's disease and hypothyroidism have been found to be associated with "certain alleles of the hR2 region of human CTLA-4 (p. 13)," and that the PMR associated with the hR2 region of CTLA4 has the sequence SEQ ID NO: 546, a 50 base pair sequence which has within it repeat consisting of 20 "AT" units p. 13-14). The parent application from which the instant application depends, 09/534061, which has been incorporated by reference, teaches that the hR2 repeat sequence is also referred to as the CTLA4 3' UTR

microsatellite repeat (p. 15 of parent application). The prior art repeatedly refers to an (AT)n repeat polymorphism in the 3'UTR of the CTLA-4 gene (for example Yanagawa *et al.*, as cited in IDS and parent application) that has been shown to be associated with Graves' disease, IDDM, and hypothyroidism (Yanagawa *et al.*, Kotsa *et al.* and Marron *et al.*, all cited in the IDS). Thus, within the human costimulatory receptor locus a polymorphism in the CTLA-4 gene has been shown to be associated with at least these autoimmune diseases, but this polymorphic repeat appears to be excluded from the scope of the instant claims.

Guidance in the Specification and Working Examples

The specification defines the costimulatory receptor locus as including the genetic region comprising the genes encoding the costimulatory receptors CD28, CTLA4 and ICOS, a region that is approximately 300 kb on chromosome 2q33. The specification provides 122 examples of PMR sequences within this region, each identified with a particular sequence identifier, and primers are given for the amplification of the sequences. The specification teaches that the elected sequence (SEQ ID NO: 354) is a PMR that is located within the CTLA4 gene (p. 12).

Furthermore, while it is noted that applicant's provide 122 putative PMR sequences that are "within the human costimulatory receptor locus," many of the rejected claims encompass the use of any PMR sequence within this locus. The specification does not define any clear ends of the locus, and thus the scope of the claims encompasses the use of PMR sequences that are upstream or downstream of the 318 kb that applicant screened, considering the possible breadth of the term "locus." These sequences are undisclosed and unpredictable. Furthermore many of the claims encompass the screening of putative polymorphic sequences which have not been demonstrated as displaying polymorphic alleles, as exemplified in example 5 where only 4 out of

25 of the tested PMR sequences demonstrated more than one allele. In order to utilize even the disclosed polymorphic sequences within the broadly claimed invention, one would have to first determine allelic variation within the PMR, which may or may not exist as these have not been screened within populations to demonstrate that the sequences referred to by applicant as PMR are in fact polymorphic within any or all human populations. It is noted that claims 15 and 16 further define the scope of the locus, and these claims additionally recite that the PMR is either within SEQ ID NO: 354 or within the CTLA4 gene.

With regard to claims 10-12 and 16 which recite determining the polymorphic variant or subtype of a PMR sequence, with claim 11 being limited to the particular sequence, while one even if one could actually practice the method steps of the claimed invention (particularly with regard to claims 11 and 12), one would not know how to use the claimed invention. That is, absent some disclosure of a relationship between the detected PMR with a disease, condition or phenotype, it would be highly unpredictable how to utilize the claimed invention, beyond as a tool to study the markers themselves.

The specification prophetically states at page 14 that "The novel polymorphic markers described herein provide additional markers that may be more closely linked with certain autoimmune disorders or conditions." However, beyond such prophetic statements, the specification does not provide any guidance concerning which alleles of which polymorphisms are associated with which autoimmune disorders or conditions. Likewise, with regard to the elected SEQ ID NO: 354 no such guidance or disclosure is provided.

Example 1 of the specification (beginning on p. 56) describes the mapping, sequencing and assembly of 2q33 section of human chromosome 2. Described is the isolation of 6 BAC

clones which were end sequenced and compiled into a hypothetical map, and compared with known GenBank sequences to order. The resulting map describes an approximately 381 kb sequence which is diagrammed in Figure 1, and referred to in the specification as the costimulatory receptor locus. Example 2 of the specification (p. 57) further discusses the features of this region and teaches that 20 potential coding sequences were identified within the region. Example 3 teaches the prediction of open reading frames using reading frame prediction programs. Example 4 (p. 59) discusses genomic microarray expression analysis to detect differentially transcribed genes within the genomic region in response to differentially treated CD4+ T cells. Clones which correspond to CTLA4 and ICOS non-transcribed regions were detected. Example 5 teaches that twenty five of the PMR sequences of the instant invention were tested for allelic polymorphism, and of these only four demonstrated polymorphisms, one of which was instant SEQ ID NO: 354 (SARA 31). Example 6 compares human ICOS to murine ICOS.

Level of Unpredictability and State of the Prior Art

The specification and the prior art provide no guidance as to which of the instantly disclosed polymorphisms are associated with which autoimmune diseases. The claims provide a list of autoimmune diseases that the instant methods can be used for determining a predisposition to, however, neither the specification nor the claims provide any guidance as to which PMR sequences are associated with which diseases. The association of a PMR sequence with a disease is highly unpredictable. There is no a priori way to predict if a given PMR sequence will be associated with any autoimmune disease at all, let alone which specific diseases, a problem which is complicated by the fact that the specification has provided no guidance as to which

alleles of the instant PMR sequences are in fact indicators of a predisposition for disease and which do not indicate a predisposition for disease. The prior art does not provide any guidance as to an association between any of these PMR sequences and autoimmune disease, nor does the prior art teach that all of the recited diseases are so associated that a single marker or set of markers could be used to indicate a predisposition to then all. Instead, the prior art teaches that in some cases even studies which examine linkage between genes and particular autoimmune diseases result in conflicting findings. Barbesino *et al.* (as cited in IDS) teach that "Discrepancies between studies may be explained by genetic differences between populations and/or by the use of different polymorphisms for the same genes (p. 1580)," thus supporting the assertion that it is highly unpredictable which PMR sequences may be associated with which autoimmmune diseases, if in fact any associations exist at all. Barton *et al.* (IDS) did not find an association between a polymorphic allele and rheumatoid arthritis. Furthermore, the prior art is replete with examples of a marker being associated with a disease in a single population but not in other test populations. For example, Shai *et al.* (1999, Human Molecular Genetics, Vol. 8, No. 4, p. 639-644) teach that a marker on human chromosome 1 is associated with Mexican American families with SLE but not in families with Caucasian ethnicity. Further, even if a particular marker is associated with one autoimmune disease in a population, it is highly unpredictable as to whether or not it will be associated with a different autoimmune disease. For example, Hatta *et al.* (1999, Genes and Immunity, Vol. 1, p. 53-60) teach an association of FcγRIIIb polymorphism with SLE in a population of Japanese patients, but no association was observed between the same polymorphism and rheumatoid arthritis. Finally, if polymorphisms that are indicative of autoimmune disorder are located in one species of organism, it is highly

unpredictable as to whether the same relationship would exist for different host organism. When discussing the mouse as a model for human SLE, Moser *et al.* (1998, PNAS USA, Vol. 95, p. 14869-14874) teach that generically in the search for disease genes causative of SLE, "Whether or not both species share any of the same susceptibility genes for lupus can only be known after the genes are identified (p. 14873)."

Quantity of Experimentation

The quantity of experimentation necessary to determine an association between any single autoimmune disease and a PMR is also quite high, requiring the screening of hundreds of patients from different populations in order to confirm the existence of a predictive association. Indeed, Epplen *et al.* (Electrophoresis, 1997, IDS) report that "Increasingly larger panels have to be screened for many different genetic markers in order to arrive at conclusions that stand the necessary statistical tests (p. 1582)." Furthermore, in the instant case, many of the claims encompass the screening of putative polymorphic sequences which have not been demonstrated as displaying polymorphic alleles, as exemplified in example 5 where only 4 out of 25 of the tested PMR sequences demonstrated more than one allele. In order to utilize even the disclosed polymorphic sequences within the broadly claimed invention, one would have to first determine allelic variation within the PMR, then one would have to determine association with disease, which association is highly unpredictable.

Conclusion

Thus, the instant claims are quite broad with regard to the autoimmune disease whose predisposition is being determined and with regard to which PMR sequences are associated with diseases and further with regard to the PMR sequences themselves. The prior art does not

provide any clear guidance to lead the practitioner in choosing the appropriate PMR-autoimmune disease combinations. The level of unpredictability is extremely high with regard to the determination of an association between any autoimmune disease and any PMR. The specification does not provide any working examples which demonstrate that the instant PMR sequences are associated with autoimmune diseases,. Finally the quantity of experimentation required to reasonably confirm the association between any single PMR and any single autoimmune disease is quite high, and the quantity of experimentation required to confirm an association between ever PMR in the human costimulatory receptor locus and every autoimmune disease is even higher. For all of these reasons, it is concluded that undue experimentation is necessary to practice the claimed invention.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1, 2, 3, 4, 5, 6, 10, 11, 12, 15, and 16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are indefinite over the recitation "wherein the PMR sequence is not an hR2 sequence," as neither the specification nor the claims define what is "an hR2 sequence," or how to identify one. The prior art is silent with respect to any sequence in the human costimulatory receptor locus that is called the hR2 sequence. With regard to hR2, the specification teaches that IDDM, Grave's disease and hypothyroidism have been found to be associated with "certain

alleles of the hR2 region of human CTLA-4 (p. 13)," and that the PMR associated with the hR2 region of CTLA4 has the sequence SEQ ID NO: 546, a 50 base pair sequence which has within it repeat consisting of 20 "AT" units (p. 13-14). The parent application, 09/534061, which has been incorporated by reference, teaches that the hR2 repeat sequence is also referred to as the CTLA4 3' UTR microsatellite repeat (p. 15 of parent application). However, none of these teachings in the specification define an hR2 sequence. It is not clear if "an hR2 seqeunce" as recited in the claims is the same as the hR2 repeat sequence, or if it is a portion of the hR2 repeat sequence or if it is any repeat sequence that has an (AT)n repeat. It is not clear if an hR2 sequence must comprise instant SEQ ID NO: 546, or does the sequence include other alleles, does it minimally have to contain SEQ ID NO: 546 but could contain additional flanking sequence, etc? Instant SEQ ID NO: 546 is largely an "AT" repeat, and it is not clear if an "hR2" sequence is any AT repeat, for example. Furthermore, it is unclear from the specification and the claims if the "hR2" sequence must be a portion of the CTLA-4 gene, or if such sequences also are in other portions of the human costimulatory receptor locus. Given this lack of definition and the use of the arbitrary term hR2 sequence, the claims are indefinite.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 10 and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Dariavach *et al.* (Eur. J. Immunol. 1988. Vol. 18, pages 1901-1905).

Dariavach *et al.* teach a method for determining the polymorphic variant or subtype of a PMR sequence in the costimulatory receptor locus in a human subject, said method comprising detecting at least one polymorphic microsatellite repeat in the CTLA4 gene of the human costimulatory receptor gene locus, wherein the PMR sequence is not an hR2 sequence.

Dariavach *et al.* sequence a 4 kb fragment comprising the CTLA4 gene. Such sequencing inherently detects any PMR within this portion of the gene. For example, there is an "at" repeat at nucleotide 417 of the first stretch of DNA in Figure 1. In this case it the repeat is two units long.

12. Claims 10, 12, and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Gyapay *et al.* (Nature Genetics, Volume 7, June 1994, pages 246-249 and 256-261).

Gyapay *et al.* teach methods for detecting microsatellite markers throughout the human genome. The methods taught by Gyapay *et al.* are via PCR employing a first primer and a second primer (see p. 248). In particular, Gyapay *et al.* teach the detection of the marker D2S307 (see p. 260-261), which the instant specification teaches is also referred to as the marker SARA 43 (see p. 57, line 29 of the instant specification), and the instant specification further teaches is within the sequence studied in the instant specification. SARA 43 amplifies a marker that starts at nucleotide 125845 (see instant specification, p. 42, second entry in table). Nucleotide 125845 is within the intergenic region between CD28 and CTLA4 (see p. 12, lines 1-2 of the instant specification. This region is considered to be within the CTLA4 gene because it is contiguous with and 5' to the CTLA4 gene. The instant specification does not define the limits of the CTLA4 gene, and indeed clearly considers PMR that are thousands of nucleotides outside of the coding region of the CTLA4 gene to be "within the CTLA4 gene (see for example,

p. 12, lines 26-29). For example, instant SEQ ID NO: 354 begins at nucleotide 263177 which is over 50,000 base pairs downstream of the "CTLA4 region" designated on page 12, line 21, but is within the list of PMR considered within the CTLA4 gene. Thus, the CTLA4 gene is fairly interpreted as containing the "CTLA4 region" as well as sequence tens of thousands of base pairs outside of this region.

Response to Remarks

Beginning at page 8 of the response, applicant addresses the rejection of claims 1-6 and 10-12 under 112 1st paragraph for lack of enablement. This rejection has been maintained and applied to newly added claims 15 and 16.

First applicant addresses the exclusion of the use of an "hR2 sequence" referring to parent application serial number 09/534061, stating that the parent application "provides the hR2 sequence in SEQ ID NO: 56." Applicant further refers to their discussion with regard to the pending 112 2nd rejection. The 112 2nd rejection is discussed in detail below.

Further arguments regarding the first paragraph rejection are provided in the response. Applicant argues that they have specifically defined the term "costimulatory receptor gene locus" to include the genetic region comprising the genes encoding CD28, CTLA4, and ICOS. This is not disputed. The specification has defined the region as INCLUDING these, but not as limited to these, as clear by the use of the language "comprising" and "including" in the definition of the region. Thus, given the language used in the specification, the claims, and in applicant's arguments, it is maintained by the examiner that the scope of the "human costimulatory receptor gene locus" encompasses regions of the genome that are not provided by applicant.

Applicant argues in the second full paragraph on page 9 that the instant specification teaches several approaches for identifying PMR sequences within the locus. However, this is not persuasive, as it is merely an invitation for one to search for additional embodiments of the claimed invention. Whether, if, and indeed where, additional PMR sequences exist within and outside of the locus as disclosed and described by applicant is highly unpredictable. Further, it is noted that while applicants have taught that they have sequenced the entire locus, they have not provided the sequence of the entire locus, only the sequence of the PMR they refer to in the specification.

Applicant states in the response that "Here, applicants have surprisingly found novel PMR markers that are more closely linked with certain autoimmune disorders or conditions." However, this statement appears to be an unsubstantiated arguments which is not supported by any evidence on the record. Applicant refers to example 5 as showing that the use of the novel PMR sequences of the invention can provide a different distribution of polymorphisms than those obtained using the hR2 marker. Example 5 teaches that twenty five of the PMR sequences of the instant invention were tested for allelic polymorphism, and of these only four demonstrated polymorphisms, one of which was instant SEQ ID NO: 354 (SARA 31). It is not clear how these polymorphisms are or are not related to the hR2 sequence distributions, and it is not demonstrated in the specification that any of these markers, nor SEQ ID NO: 354 in particular, are associated with or indicative of any disease, or all human autoimmune disease.

Applicant states that the examiner is requiring a working example for every claimed embodiment. This is not the case. The 112 1st paragraph rejection is based on an analysis of all of the Wands factors, and in this analysis it is agreed that working examples in the specification

is one of the factors. In this case the lack of working examples in the specification is one factor used to support the conclusion of lack of enablement.

Applicants specifically traverse the rejection of claims 10-12 stating that it is well known that polymorphisms in the 3'UTR of CTLA4 have been linked to a number of autoimmune genetic diseases. However, as discussed in the rejection, it is highly unpredictable if or how this previous knowledge in the art would apply to any of the instantly disclosed PMR, some of which have not even been demonstrated to be polymorphic, and indeed were demonstrated in example 5 to NOT be polymorphic in the sample population. Applicant further argues that these elements can be used to further refine genetic alleles, however, again, it is highly unpredictable if or how this previous knowledge in the art would apply to any of the instantly disclosed PMR, some of which have not even been demonstrated to be polymorphic. The scope of the claims include the use of any markers within the CTLA-4 gene, and the specification does not demonstrate any association between any of these and any disease or phenotype. The specification has only shown that alleles exist. Absent any knowledge of their close linkage to predictive alleles, the practice of the claimed invention would be highly unpredictable as to how to use any information gained from the claimed genotyping methods.

Thus, for these reasons, the rejection is maintained and applied to newly added claims 15 and 16.

In the discussion of the 112 2nd paragraph rejection (beginning on p. 11 of the response), applicant recites a section of the parent application. The cited section refers to an "hr2 segment" which is parenthetically noted as nucleotides 6561-6623 of SEQ ID NO: 56. This is a 63 nucleotide sequence. However, this is not a clear definition of an "hR2 sequence" as recited in

the claims, especially in light of other portions of the instant specification which provides a conflicting description of the "hR2 region." For example, the instant specification teaches that IDDM, Grave's disease and hypothyroidism have been found to be associated with "certain alleles of the hR2 region of human CTLA-4 (p. 13)," and that the PMR associated with the hR2 region of CTLA4 has the sequence SEQ ID NO: 546, a 50 base pair sequence which has within it repeat consisting of 20 "AT" units (p. 13-14). However, none of these teachings in the specification define an "hR2 sequence" in particular, as is recited in the claims. Thus, it is not clear if "an hR2 seqeunce" is the same as the hR2 repeat sequence referred to in the parent application and cited in the response, or if it also encompasses only a portion of the hR2 repeat sequence or if it is any repeat sequence that has an (AT)n repeat. It is not clear if an hR2 sequence must comprise instant SEQ ID NO: 546, or the cited portion of instant SEQ ID NO: 56 in the parent application, or if an hR2 sequence includes other alleles, or does it minimally have to contain SEQ ID NO: 546 but could contain additional flanking sequence, etc? Instant SEQ ID NO: 546 is largely an "AT" repeat, and it is not clear if an "hR2" sequence is any AT repeat, for example. Furthermore, it is unclear from the specification and the claims if the "hR2" sequence must be a portion of the CTLA-4 gene, or if such sequences also are in other portions of the human costimulatory receptor locus. Thus, for these reasons, the rejection is maintained and applied to newly added claims 15 and 16.

The rejection of claim 10 under 35 U.S.C. 102(b) as being anticipated by Weber (US 5582979) is WITHDRAWN in view of the amendment of claim 10 to require that the PMR is within the CTLA4 gene of the human costimulatory receptor gene locus. The microsatellite within the D2S72 locus does not appear meet this limitation (i.e. the examiner could not

determine where in the human costimulatory receptor gene locus is located). A new rejection is set forth to address the amended claims.

Conclusion

13. No claims are allowed.

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Monday through Friday, from 9:00 AM until 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached by calling (571) 272-0745.

The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-0507.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Juliet C. Switzer
Primary Examiner
Art Unit 1634

January 4, 2005